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Pharmaceutical Formulation	
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8a Please fill in the number of sheets for each of the following types of document contained in this application

Claims 4 Specification 12

Abstract

Drawing(s) 2 only (1)

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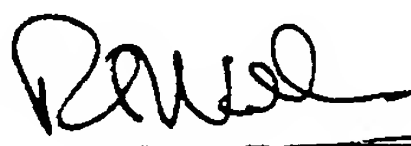
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Dated 29 July, 1999

Ralph Francis Walker

Agent for the Applicant

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Pharmaceutical Formulation

The invention relates to pharmaceutical formulations, being a multi-compartment pharmaceutical capsule formulation.

5 Pharmaceutical capsules are well known, generally being intended for oral administration. Such capsules generally comprise an envelope wall of a pharmaceutically acceptable, e.g. orally ingestible, polymer material such as gelatin, although other materials for capsule walls, e.g. starch and cellulose based polymers

10 are also known. Such capsules generally have soft walls made by making a film on a capsule former, which is then allowed to dry. Rigid walled capsules made by injection moulding are also known, see for example US 4576284, US 4591475, US 4655840, US 4738724, US 4 738817 and US 4790881 (all to Warner Lambert). These disclose specific constructions of capsules made of gelatin, starch and other polymers, and methods of making them by injection moulding of hydrophilic

15 polymer – water mixtures. US 4576284 specifically discloses such capsules provided with a cap which closes the capsule, and which is formed in situ on the filled capsule by moulding. US 4738724 discloses a wide range of rigid capsule shapes and parts.

20 Multi-compartment capsules, including those of the type where each compartment has different drug release characteristics or for example contains a different drug substance or formulation are also known, for example in US 4738724 (Warner-Lambert), US 5672359 (University of Kentucky), US 5443461 (Alza Corp.), WO 9516438 (Cortecs Ltd.), WO 9012567 (Helminthology Inst.), DE-A-3727894, BE 900950 (Warner Lambert), FR 2524311, NL 7610038 (Tapanhony

25 NV), FR 28646 (Pluripharm), US 3228789 (Glassman), US 3186910 (Glassman).

It is an object of this invention to provide an alternative and for some applications improved multi-compartment capsule construction which provides *inter alia* improved manufacturing convenience and greater flexibility in producing a dosage form adapted to a patient's specific administration requirement.

30 Other objects and advantages of the invention will be apparent from the following description.

According to this invention a pharmaceutical dosage form comprises a plurality of capsule compartments each bounded and physically separated from at least one adjacent compartment by a wall made of a pharmaceutically acceptable polymer material, adjacent compartments being connected together in the assembled dosage form and being retained together by the connection at least prior to administration to a patient, one or more of the compartments containing a drug substance.

The connectable nature of these capsule compartments advantageously enables various compartments to be assembled and connected together to produce a dosage form, the respective compartments having different characteristics and/or contents. By the use of common connectable parts the compartments of the invention may be assembled in various combinations.

The invention also provides individual capsule compartments adapted for use in the assembled dosage form.

Suitably in the assembled dosage form there are at least two, for example, three compartments. Three or more such compartments may be linearly disposed in the assembled dosage form, e.g. in an arrangement comprising two end compartments at opposite ends of the line, and one or more intermediate compartments.

In the assembled dosage form the adjacent compartments may be connected together by any suitable means. Preferably the adjacent compartments are connected together by means of a weld, e.g. a thermal weld or preferably an ultrasonic or inductive weld, adhesive (e.g. curable adhesives such as UV curable adhesives), between adjacent parts of the wall of the adjacent compartments. This weld may be achieved by bringing compartments into adjacent contact and applying an adhesive, localised heating e.g. inductive heating or an ultrasonic horn (suitable types are commercially available and will be apparent to those skilled in the art) to the region of contact. Adjacent compartments may have substantially planar regions of their surface which may be brought into contact and then the weld may be formed, or may have regions of their surface of complementary shapes, thereby facilitating close contact between the respective complementary surfaces of the compartments.

Additionally or alternatively adjacent compartments may be provided with respectively connectable first and second connectable parts such that the first part on one compartment may connect with the second part on an adjacent compartment.

These connectable parts may facilitate bringing the adjacent compartments together in a suitable configuration, e.g. into the above-mentioned linear configuration. The connectable parts may be such as to facilitate the assembly together of the compartments in preferred configurations, e.g. the connectable part(s) on one compartment may be such as to only connect with a corresponding part on other

selected compartments, but not with non-corresponding connectable parts on other compartments. The connectable parts may also be such that the connection between the first and second connectable parts on adjacent containers contributes to the retention of the adjacent compartments together, e.g. via a retaining friction, snap, screw or other kind of fit between the connectable parts.

For example in one embodiment the respective first and second connectable parts may be respectively interlocking parts. For example the first or second part may be a female socket part, and the corresponding second connecting part may be a corresponding male part which fits into the female socket with a retaining friction, snap, screw or other kind of interlocking fit.

In a friction fit for example the male part may be slightly larger than the female socket such that force needs to be applied against the natural resilience and contact friction of the male and female parts to cause the male part to enter the female socket, and similar force needs to be applied to separate them. In a snap fit for example the male and female parts may be provided with a concavity and a corresponding convexity, such as a ridge and groove, which lock together as the parts are forced together against the natural resilience of the parts. Such a ridge and groove may for example comprise a co-operating circumferential or part circumferential bead and groove, for example located about the circumference of a connectable male and female part.

Above-mentioned US 4576284 and US 4738724 for example, the contents of which are included herein in their entirety by way of reference, disclose a range of interlocking parts of this general type by means of which capsule compartments may be made to interlock together. See for example Figs. 1, 2 and 3 of US 4576284

which discloses interlocking parts by means of which a cap may be retained on the mouth of a capsule, and Figs. 4 – 43 of US 4738724 which disclose numerous interlocking parts by means of which part capsule shells may interlock and be retained together as an assembled complete capsule.

5 For example in a dosage form of the invention comprising a linear disposition of compartments, the or each intermediate compartment(s) may be provided with one or more connectable parts, which may connect with one or more connectable parts on an adjacent intermediate compartment and/or with one or more connectable parts on an adjacent end compartment. Also the end compartment(s)
10 may be provided with one or more connectable parts which may connect with connectable parts on an adjacent intermediate compartment and/or with one or more connectable parts on another end compartment. By means of this two end compartments may connect together in a two-compartment dosage form, or two end compartments may be connected to one or more intermediate compartments. By
15 using common first and second connectable parts on the compartments the various end and intermediate compartments may be made such that they may be connected together in various combinations of assembled dosage forms.

 In one embodiment one or more, e.g. all, of the compartments may for example be substantially cylindrical, which term includes shapes which have a
20 circular, oval or oblate circular cross section across the longitudinal axis. The compartments may for example be substantially tub-shaped, i.e. having a base closed by a base wall, and side walls extending upward from the base wall, and an upper open mouth. With such a construction the compartments may connect together by the base of a first compartment fitting into the open mouth of an
25 adjacent second compartment, so as to close the mouth of the second compartment, and such that the base wall of the first compartment physically separates the first and second compartments.

 For example in the above described tub-shaped compartments the base part of the first compartment may comprise a male part and the mouth opening of the
30 second compartment may comprise a corresponding female socket. The base part of the first compartment may be shaped to fit in this way into the mouth opening of the second compartment. A weld between the compartments may then be formed in the

region of contact between the base of the first compartment and the mouth of the second compartment. Additionally or alternatively for example the respective base part and mouth opening may be provided with connectable parts to enable a retaining friction, snap, screw or other kind of interlocking fit.

5 In such an assembly, clearly only one of the end compartments can have its mouth opening closed by the base wall of an adjacent compartment, and the other end compartment will require some other type of closure for its mouth opening. The closure may for example be made from the same, or a different, polymer than the polymer material of the compartment. This closure may for example comprise an
10 over-cap for example fitting snugly and tightly around the outer surface of the side walls of the compartment, as in the general manner disclosed in US 4196565 or US 4250097 (both Capsugel AG) or alternatively the closure may comprise a plug type of closure. Above-mentioned US 4576284 discloses some suitable types of closure for capsule compartments which are suitable for use with the present invention. The
15 closure and mouth opening may be retained in place on the mouth opening of their compartment, or additionally or alternatively they may be provided with features to enable a retaining friction, snap, screw or other kind of interlocking fit.

Alternative ways of assembling the compartments are encompassed within the scope of the invention.

20 For example rather than having an open mouth which is closed by the presence of an adjacent compartment, one or more of the compartments may be made closed and for example containing the drug substance, and may in this closed form connect in the manner described above with the one or more adjacent compartments.

25 For example one or more of the compartments may be made in the form of two part compartment shells, each part compartment shell comprising a closed end and side walls and having a mouth opening opposite the closed end, which connect together, e.g. by the means discussed above, with their mouth openings facing, to form the capsule compartment. One or both of the closed ends may connect with an
30 adjacent compartment, e.g. by the means discussed above. For example if the dosage form comprises a linear assembly of compartments one or both closed ends of the intermediate compartment(s) may be connectable to an end compartment. For

example the end compartment may be substantially tub-shaped as described above and may have a mouth opening that is connectable to the closed end in the manner described above.

The wall of the compartments may be made of any pharmaceutically acceptable polymer which is capable of being formed, e.g. by an injection moulding process, into the required shape. Suitable polymer materials include: polyvinyl alcohol (PVA), natural polymers (such as polysaccharides like pullulan, carrageenan, xanthan or agar gums), Polyethylene glycols (PEG), hydroxypropylmethylcellulose (HPMC), methylcellulose, hydroxyethylcellulose, hydroxyethyl methylcellulose, hydroxypropylcellulose, methacrylic acid copolymer (such as Eudragit ETM, Eudragit LTM and/or Eudragit STM), ammonium methacrylate copolymers (such as Eudragit RLTM and/or Eudragit RSTM), carboxymethylcellulose, povidone (polyvinyl pyrrolidone), polyglycolysed glycerides (such as Gelucire 44/14TM, Gelucire 50/02TM, Gelucire 50/13TM and Gelucire 53/10TM), carboxyvinyl polymers (such as CarbopolsTM), polyoxyethylene-polyoxypropylene copolymers (such as Poloxamer 188TM).

Preferred polymers are orally ingestible polymers and include polyvinyl alcohol, hydroxypropyl methyl cellulose, and other cellulose-based polymers. Preferred polymers also include polymer materials which preferentially dissolve or disintegrate at different points in the digestive tract, e.g. Eudragit ETM which preferentially dissolves in the more acid pH of the stomach, or enteric polymers such as Eudragit LTM and/or Eudragit STM, which preferentially dissolve in the more alkaline pH of the intestine. Preferred polymers also include polymers which dissolve slowly, e.g. a predetermined rate in the digestive tract, such as Eudragit RLTM and/or Eudragit RSTM.

The polymer material(s) may include other substances to modify their properties and to adapt them to various applications, including for example the following general classes of substances. Surfactants, such as Polysorbate 80TM, sodium lauryl sulphate, and Polyoxyl 40TM hydrogenated castor oil. Absorption enhancers, such as LabrasolTM, TranscutolTM; glidants, such as talc, magnesium stearate, silicon dioxide, amorphous silicic acid, fumed silica, SimeticoneTM; plasticizers, such as triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl

tributyl citrate, diethyl phthalate, dibutyl phthalate, propylene glycol, triacetin and castor oil; substances for release modification, such as ethyl cellulose and cellulose acetate phthalate; disintegrants, such as sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolodone), colouring agents, 5 flavouring agents and sweetening agents.

The compartments may for example be made from such polymer materials using conventional injection moulding processes, i.e. in which a fluid polymer is injected under pressure into a precisely made die cavity in a mould block. Injection 10 moulding processes enable the compartments to be made with the precision necessary to achieve tight friction-fit or snap-fit interlocking. Suitable techniques of injection moulding are known from for example the art of manufacture of small plastic components e.g. small parts of LEGO™ toys.

Consequently the invention also provides a moulding process, for example an injection moulding process, wherein capsule compartments of the dosage form 15 are made. The invention also provides a mould, for example an injection mould suitable for use in this moulding process. Such a mould may have a mould cavity corresponding to the external shape of the capsule compartment.

The dimensions and shape of each of the compartments and hence of the overall assembled dosage form may be determined by the nature and quantity of the 20 material to be contained therein and the intended mode of administration and intended recipients. For example a dosage form intended for oral administration may be of a shape and size similar to that of known capsules intended for oral administration.

The dosage form of this invention enables the assembly together of 25 compartments which differ in their drug content and/or drug content release characteristics to provide a dosage form tailored to specific administration requirements, or to rapid prototyping of dosage forms.

For example two or more compartments may each contain different drug substances, and/or different drug substance formulations, so that a combination of 30 two or more drug substances or formulations may be administered to a patient.

The dosage form is particularly suitable for presentation as an oral dosage form containing one or more drug substances suitable for oral administration.

The dosage form is suitable for all types of drug substance, and the drug substance(s) contained in any compartment may be present in any suitable, e.g. conventional, form, e.g. as a powder, granules, compact, microcapsules, gel syrup or liquid provided that the wall material is inert to the liquid content of the latter three forms. The contents of the compartments, e.g. drug substances, may be introduced into the compartments by standard methods such as those used conventionally for filling capsules, such as dosating pins or die filling.

The compartments may contain combinations of drug substances in powder, granule, compact, gel, syrup or liquid form, provided that the drug substance and the polymer capsule compartment wall are inert relative to each other. For example two or more compartments may contain the same or different drug substances(s) or drug substances in different forms, such as those before mentioned.

The compartments may differ from each other in their drug content release characteristics, and this may be achieved in various ways.

For example one or more compartments may be substantially immediate release, i.e. releasing their drug content substantially immediately upon injection or on reaching the stomach. This may for example be achieved by means of the compartment wall dissolving, disintegrating or otherwise being breached to release the drug content substantially immediately. In the case of the above-described linear arrangement of compartments, suitably one of the end compartments may be a substantially immediate-release compartment, so that the disruption of this end compartment has little or no influence on the other compartments, e.g. the other end compartment or the intermediate compartment(s), in the assembly. In such a case the other end compartment and the intermediate compartment(s) may be delayed release compartments, i.e. releasing their drug content at a delayed time after administration. For example in the case of oral administration these delayed release compartments may release their drug content in the stomach, small or large intestine.

Determination of the time or location within the gastro-intestinal tract at which a compartment releases its drug content may be achieved by for example the nature of the compartment wall material, or in the case of an end compartment closed by a closure the nature of the closure material. For example the wall of

different, e.g. adjacent and/or non-adjacent compartments may be made of polymers which are different or which otherwise differ in their dissolution or disintegration characteristics so as to endow different compartments with different drug release characteristics.

- 5 For example the wall or closure material may be a polymer which dissolves or disperses at stomach pH to release the drug substance in the stomach. Alternatively the wall material of different compartments may differ so that different compartments have different release characteristics.

-
- 10 For example a compartment may have a wall or a closure comprising an enteric polymer which dissolves or disperses at the pH of the small or large intestine to release the drug substance in the intestine. Suitable such polymers have been described above.

- 15 Additionally or alternatively the wall material may differ in thickness between compartments so that thicker walled compartments disrupt more slowly than thinner walled compartments.

- 20 Additionally or alternatively the compartment walls or the closure may have areas or points of weakness which preferentially dissolve and determine the time of onset and/or rate of release of the drug substance content. For example such points of weakness may comprise holes, e.g. small holes, e.g. laser-drilled holes in the compartment wall or the closure, these holes being closed and/or covered with a film of a polymer material, which dissolves at a pre-selected point in the digestive tract, e.g. an enteric polymer.

The invention will now be described by way of example only with reference to:

- 25 Fig.1 which shows a longitudinal sectional view of a dosage form of the invention assembled together.

Fig. 2 which shows a longitudinal sectional view of another dosage form of the invention assembled together.

- 30 Referring to Fig. 1, a dosage form 1 is shown comprising three compartments 2, 3, 4 linearly disposed in the assembled dosage form, in an arrangement comprising two end compartments 2, 4 at opposite ends of the line, and one intermediate compartment 3. All of the compartments 2, 3, 4 are

substantially cylindrical but with an oval cross section across the longitudinal axis. The compartments 2, 3, 4 are substantially tub-shaped, i.e. each having a base closed by a base wall 2A, 3A, 4A, and each having side walls 2B, 3B, 4B extending upward from the base wall 2A, 3A, 4A, and an upper open mouth. Each of the
5 compartments 2, 3 and 4 is made of a polymer such as polyvinyl alcohol polymer by injection moulding.

The compartments connect together by the base 2A, 3A of a first compartment 2, 3 fitting into the open mouth of an adjacent second compartment
10 respectively 3, 4 so as to close the mouth, and such that the base wall 2A, 3A of the first compartment 2, 3 physically separates the first and second compartments 2, 3 and 4. In this assembly of compartments 2, 3, 4 the base part of an upper compartment 2, 3 comprises a male part and the mouth opening of a lower compartment respectively 3, 4 comprises a female socket.

Compartment 4 is an end compartment and has its mouth opening closed by
15 the base wall 3A of compartment 3. The other end compartment 2 is closed by a closure 5 having a plug part 6 which is dimensioned to fit into the mouth opening of the compartment 2.

The base parts 2A and 3A, and the plug part 6, fit into the respective mouth openings of the compartments 3, 4 and 2. A weld is formed between the base parts
20 2A and 3A, the plug part 6, and the respective mouth openings of the compartments 3, 4 and 2, for example by the application of local heating or an ultrasonic horn (not shown) to the region where these parts are in contact. Each of the base parts 2A, 3A, and the plug part 6, and the corresponding mouth openings of the compartments 3, 4 and 2 may additionally or alternatively be provided with features
25 (not shown) such as a convex circumferential bead and a corresponding circumferential groove into which the bead may fit, such that the base part 2A, 3A and mouth openings of the compartments 3 and 4, and the plug part 6 and mouth opening of compartment 2 may connect together by a snap fit interlocking engagement overcoming the natural resilience of the polymer material of the base
30 part and mouth opening.

The base parts 2A, 3A, 4A of the compartments and the mouth openings of the compartments 2, 3, 4, and the plug part 6 are all of common dimensions so that

the compartments 2, 3 and 4 may be fitted together in other linear combinations, and so that the plug 5 may be used to close the mouth opening of any of the other compartments 2, 3 or 4.

Similarly, two or more than the three compartments 2, 3 or 4, may be
5 connected together in an analogous manner to that shown in Fig 1.

Fig. 2 shows another dosage form assembly 1. This assembly 1 also comprises three compartments 7, 8, 9 in a linear assembly of two end compartments 7, 9 and an intermediate compartment 8. The intermediate compartment 8 is made in the form of part compartment shells 8A and 8B, each part shell 8A, 8B
10 comprising a closed end 8C and 8D and side walls 8E and 8F, with a mouth opening opposite the closed end. The mouth openings of the two part shells 8A and 8B are each provided respectively with a male connectable part 10 and a female connectable part 11. These part shells 8A, 8B connect together with their respective male and female parts 10 and 11 connecting to form the capsule compartment 8.
15 Both of the closed ends 8C, 8D are externally provided with connectable parts 12, 13.

Each end compartment 7, 9 is in the form of a tub-shaped compartment and has a mouth opening, e.g. 14 being that of compartment 7, which comprises a female part that corresponds in shape with the connectable parts 12, 13 on the
20 intermediate compartment 8 to connect the assembly 1 together.

As with the dosage form of Fig. 1, a weld is formed between the parts 10, 11, 12, 13 and the respective mouth openings of the compartments 7 and 9, by the application of local heating or an ultrasonic horn (not shown) to the region where these parts are in contact. Each of these parts 10, 11, 12, 13 and the respective
25 mouth openings of the compartments 7 and 9 may additionally or alternatively be provided with features (not shown) such as respectively a convex circumferential bead and a circumferential groove into which the bead may fit, such that these interlocking parts may connect together by a snap fit engagement.

Each of the compartments 2, 3, 4, 7, 8 and 9 in Figs 1 and 2 may be made
30 of the same or different polymer and may have the same or different drug release characteristics. The intermediate compartments 3 and 8 respectively of Figs. 1 and 2 are more suitable for a modified release compartment, as dissolution or disruption

of the end compartments 2, 4, 7 and 9 before the intermediate compartments 3 and 8 can occur without disturbance of these intermediate compartments.

Each of the compartments 2, 3, 4, 7, 8 and 9 in Figs 1 and 2 contains the same or different drug substance and/or formulation. This may for example be in the form of powder, granulates, or other solid forms. Alternatively the compartments may contain liquid, gel etc. formulations (not shown).

Claims:

1. A pharmaceutical dosage form which comprises a plurality of capsule compartments each bounded and physically separated from at least one adjacent compartment by a wall made of a pharmaceutically acceptable polymer material, adjacent compartments being connected together in the assembled dosage form and being retained together by the connection at least prior to administration to a patient, one or more of the compartments containing a drug substance.
2. A dosage form according to claim 1 wherein there are three compartments linearly disposed in the assembled dosage form in an arrangement comprising two end compartments at opposite ends of the line, and one or more intermediate compartments.
3. A dosage form according to claim 1 or 2 wherein the adjacent compartments are connected together by means of a weld between adjacent parts of the wall of the adjacent compartments.
4. A dosage form according to any one of the preceding claims wherein adjacent compartments are provided with respectively connectable first and second connectable parts such that the first part on one compartment may connect with the second part on an adjacent compartment.
5. A dosage form according to any claim 4 wherein the connectable part(s) on one compartment may be such as to only connect with a corresponding part on other selected compartments, but not with non-corresponding connectable parts on other compartments.
6. A dosage form according to claim 4 or 5 wherein the connectable parts are such that the connection between the first and second connectable parts on adjacent containers contributes to the retention of the adjacent compartments together.

7. A dosage form according to any one of claims 4, 5 or 6 wherein the respective first and second connectable parts are respectively interlocking parts.

8. A dosage form according to any one of the preceding claims comprising a linear disposition of compartments, the or each intermediate compartment(s) being provided with one or more connectable parts, which may connect with one or more connectable parts on an adjacent intermediate compartment and/or with one or more connectable parts on an adjacent end compartment.

9. A dosage form according to claim 8 wherein the end compartment(s) are provided with one or more connectable parts which may connect with connectable parts on an adjacent intermediate compartment and/or with one or more connectable parts on another end compartment.

10. A dosage form according to any one of the preceding claims wherein the compartments are substantially tub-shaped having a base closed by a base wall, and side walls extending upward from the base wall, and an upper open mouth.

11. A dosage form according to claim 10 wherein the compartments connect together by the base of a first compartment fitting into the open mouth of an adjacent second compartment, so as to close the mouth of the second compartment, and such that the base wall of the first compartment physically separates the first and second compartments.

12. A dosage form according to claim 10 or 11 wherein the base part of the first compartment comprises a male part and the mouth opening of the second compartment comprises a corresponding female socket.

13. A dosage form according to any one of claims 1 to 9 wherein one or more of the compartments is/are made closed and for example containing the drug substance, and may in this closed form connect with one or more adjacent compartments.

14. A dosage form according to any one of claims 1 to 9 wherein one or more of the compartments is made in the form of two part compartment shells, each part compartment shell comprising a closed end and side walls and having a mouth opening opposite the closed end, which connect together with their mouth openings facing, to form the capsule compartment.
15. A dosage form according to claim 14 wherein one or both of the closed ends may connect with an adjacent compartment.
16. A dosage form according to claim 15 which comprises a linear assembly of compartments one or both closed ends of the intermediate compartment(s) being connectable to an end compartment.
17. A dosage form according to any one of the preceding claims wherein the compartments are made of polyvinyl alcohol, hydroxypropyl methyl cellulose, other cellulose-based polymers, or polymer materials which preferentially dissolve or disintegrate at different points in the digestive tract.
18. A dosage form according to any one of claims 1 to 17 wherein two or more compartments each contain different drug substances, and/or different drug substance formulations.
19. A dosage form according to any one of claims 1 to 18 wherein the compartments differ from each other in their drug content release characteristics.
20. A dosage form according to claim 19 wherein the wall of different compartments are made of polymers which are different or which otherwise differ in their dissolution or disintegration characteristics so as to endow different compartments with different drug release characteristics.

21. A dosage form according to claim 20 wherein one or more compartments are substantially immediate release.

5 22. A dosage form according to claim 21, being a linear arrangement of compartments and one of the end compartments being a substantially immediate-release compartment.

23. A dosage form according to claim 22 wherein the other end compartment or the intermediate compartment(s) in the assembly are delayed release compartments.

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24. A moulding process wherein capsule compartments of a dosage form according to any one of the preceding claims are made.

25. A mould suitable for use in the moulding process of claim 24.

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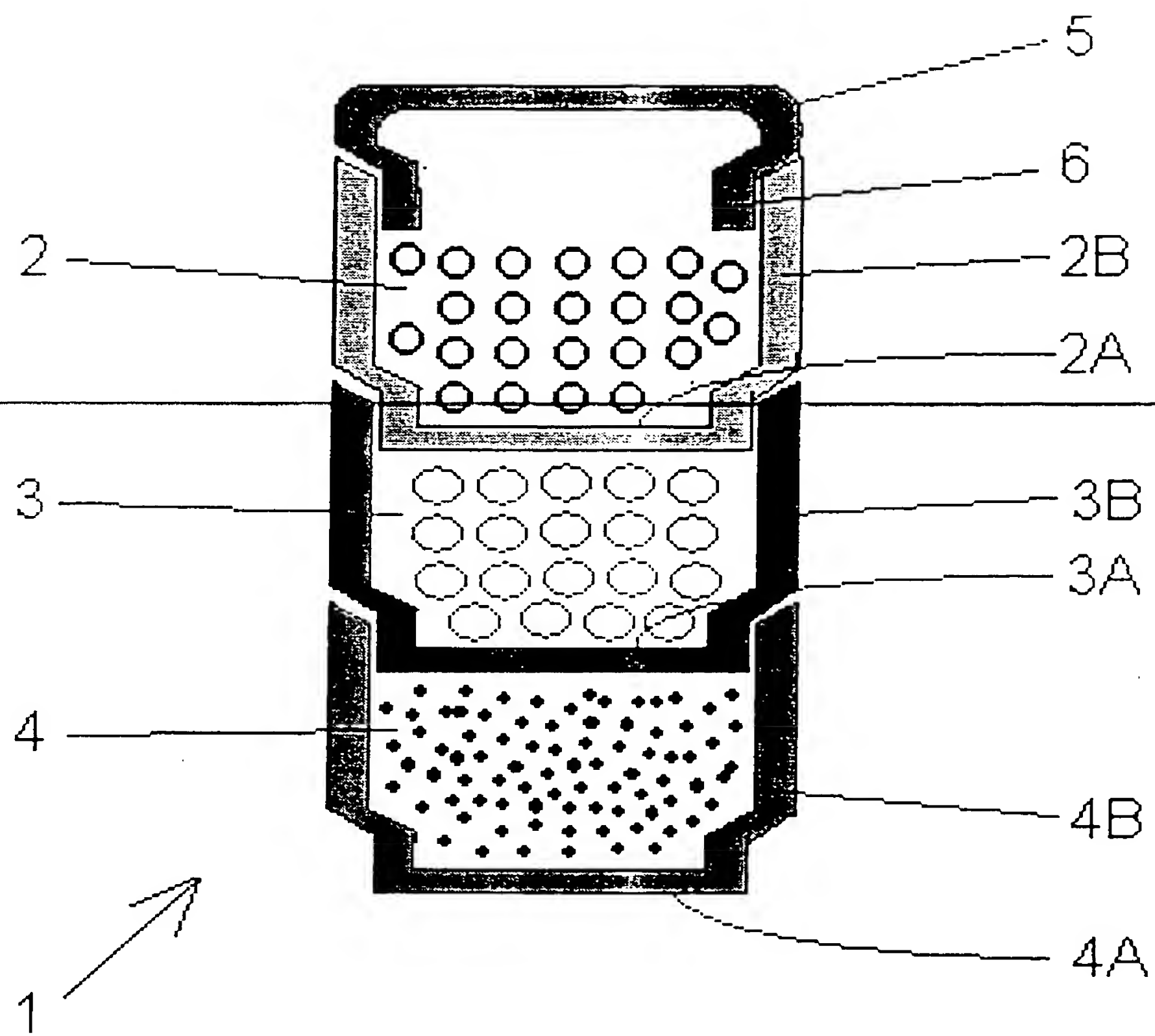


Fig. 1

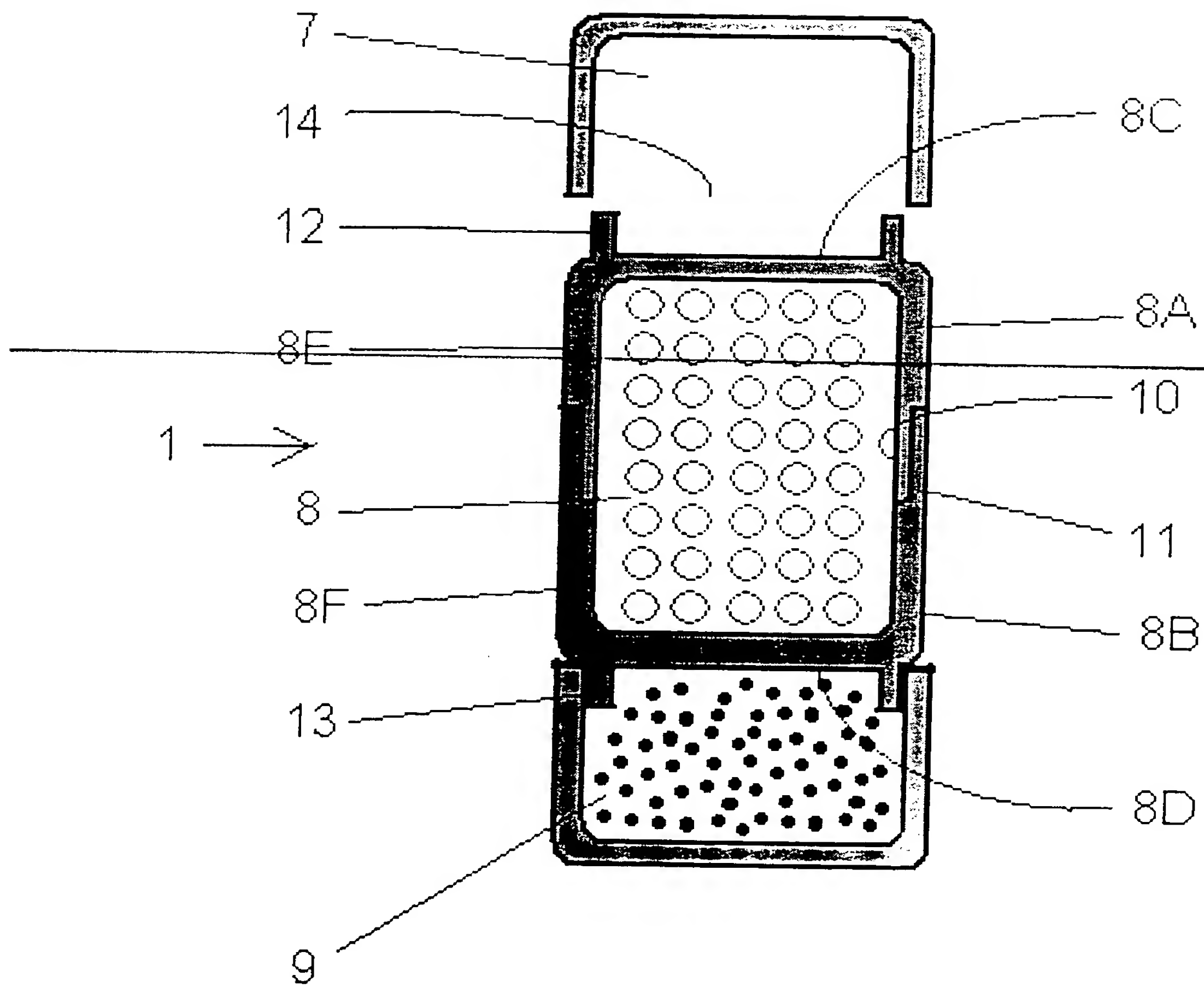


Fig. 2